

## MODEL DEVELOPMENT AND SENSITIVITY ANALYSIS FOR BLOOD GLUCOSE DYNAMICS BASED ON SHORT INSULIN TOLERANCE TEST

A. G. Ibrahim<sup>1</sup>, A. A. Hamisu<sup>2</sup> and L. C. Edomwonyi-Otu<sup>2</sup>

<sup>1</sup>Federal University Wukari, Taraba State, Nigeria

<sup>2</sup>Chemical Engineering Department, Ahmadu Bello University, Zaria, Nigeria)

Corresponding author's email: [alamin446@gmail.com](mailto:alamin446@gmail.com)

### Abstract

Biological systems usually consist of large number of components and involve processes at a variety of spatial, temporal and biological scales. Systems biology aims to understand such systems by integrating information from all functional levels into a single dynamic model. This study discusses model development and the use of Global Sensitivity Analysis (GSA) in systems biology modeling and shows how the information content of clinical data from Short Insulin Tolerance Test (SITT) can be handled by optimal model-based estimation techniques. The goal is to develop dynamic model for type II diabetes and estimate set of parameters of the model with greater accuracy and precision. Based on the SITT data, the blood glucose dynamic model was developed as a system of linear differential equations with constant coefficients (parameters). The sensitivity of the parameters was tested using a novel GSA based approach, Derivative-Based Global Sensitivity Measures (DGSM). The proposed approach was implemented in SensSB (a Matlab based toolbox). For the purpose of comparison, the sensitivity of the model was also tested using Sobol's method and a local approach. The results have shown that the model is less sensitive to the third parameter  $K_2$  and fits the SITT data satisfactorily.

**Keywords:** Sensitivity analysis, Biological systems, SITT data, Blood glucose concentration model, Cramer-Rao statistical method

### 1. Introduction

Sensitivity analysis (SA) generally is the study of how the uncertainty in the output of a mathematical model or system can be apportioned to different sources of uncertainty in its inputs (Pannell 1997). The SA methods are used to determine the influence of uncertainty factors in the output of a model. They also indicates which of the uncertainty factors need to be further examined in order to reduce uncertainty (Saltelli and Tarantola, 2006). SA algorithms were applied in physics (Pastorelli *et al.*, 2000), chemistry (Saltelli and Tarantola, 2006), social sciences, and many others. However, fewer techniques have been exploited in the field of biomedical engineering (Hu and Shi, 2010). SA methods are classified into local methods (LSA) and Global methods (GSA). In LSA, inputs are varied one at a time by a small amount around some fixed point and the effect of individual perturbations on the output is calculated. GSA on the other hand, allows variation of all inputs simultaneously over their entire input space. Specifically GSA uses a sampling-based approach, and the effects on the output of both individual inputs and interactions between inputs are assessed (Sumner 2010). The advantageous characteristic of GSA methods is that they are independent of model characteristic such as linearity between the outputs and inputs of the model (Buis *et al.*, 2010).

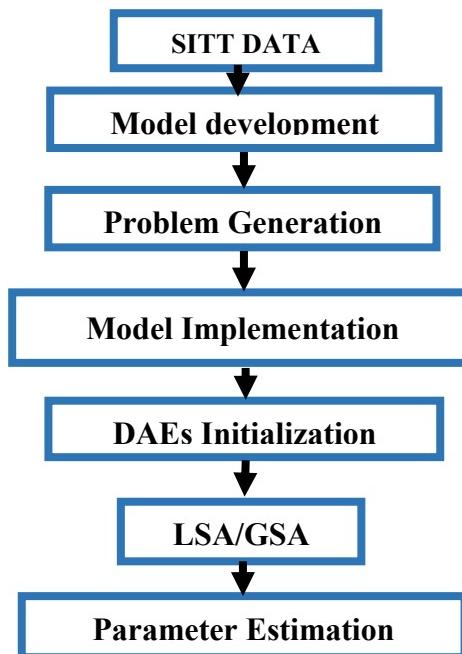
SA was used in mathematical modeling in many areas including biological model formulations (Hetherington *et al.*, 2006). The most common example of SA in biological system is the use of metabolic control analysis (MCA) in the study of metabolism (Sumner 2010). However, it was less commonly used in other areas of biology such as cellular signaling (Hu and Yuan, 2006).

Model identification system describe a dynamic behavior of a system or process in either the time or frequency domain. Most of the models used in blood glucose concentration identification are Auto-Regressive models with exogenous inputs (ARX) to represent unknown dynamic of blood glucose concentration (Isuru *et al.*, 2015). Recently, adaptive system identification techniques have been used for prediction of blood glucose concentration to minimize hypoglycemia (Eren-Oruklua *et al.*, 2012). In this paper, a dynamic model was identified and sensitivity analysis technique was applied on blood glucose concentration model for type II diabetes with the view to estimating a set of parameters of the model with reasonable degree of accuracy and precision.

## 2. Material and Methodology

The Short insulin Tolerance Test (SITT) was conducted at the General Out-Patients Department (GOPD) of University of Lagos Teaching Hospital by Fasanmade (1987), adhering strictly to regulation for use of human subjects as reported by Gutti *et al.* (2010), Unlike in Gutti *et al.* (2010), here, the data was classified into parameters and control variables and stored in matrix G with the amount of insulin injected as input variable (manipulated variable). Also, the data were rearranged and reshaped into a single column such that it can represent the output of the model.

The procedure followed in model development and sensitivity analysis on blood glucose concentration model is shown in Figure 1.



**Figure 1:** Procedure for Model development and sensitivity analysis.

### 2.1 Problem Generation

The interaction of blood glucose concentration in human body can be formulated based on the law of conservation of mass, as follows:

$$\text{Rate change} = \text{in} - \text{out} \quad (1)$$

From Equation (1) above, the rate change of glucose concentration can be written as

$$\text{Rate change of glucose concentration} = \text{Glucose}_{\text{in}} - \text{Glucose}_{\text{out}} \quad (2)$$

The rate change of glucose concentration is determined by insulin-independent glucose uptake in which the SITT was conducted on patients with non-insulin dependent diabetes mellitus within the age range of 25-60 years as reported in Gutti *et al.* (2010).

Let  $G_1$  denote the amount of glucose concentration in the body and  $G_2$  denotes the blood glucose concentration at time  $t \geq 0$ . From the information available, assuming the reaction kinetics follows first order, Equation (2) can be mathematically written as:

$$\frac{dG_1}{dt} = -k_1 G_1 \quad (3)$$

$$\frac{dG_2}{dt} = k_1 G_1 - k_2 (G_2 - G_0) \quad (4)$$

where:  $G_1$  (mg/dL) is the glucose concentration in the body,  $G_2$  (mg/dL) is the plasma blood glucose concentration,  $G_0$  is the initial blood glucose concentration during the fasting period (baseline value) at  $t = 0$ . The initial condition are  $G_1(0) = G_2(0) = G_0$ , the rate constant  $K_1$  ( $\text{min}^{-1}$ ) is the rate of glucose absorption and  $K_2$  ( $\text{min}^{-1}$ ) is the rate of disappearance of glucose and  $t$  is the time taken during the experiment (min). Equations (3) and (4) represent the glucose-insulin system following the short insulin tolerance test (SITT). Note that in Equation (3), the short insulin tolerance test was done during fasting and there was no flow of glucose into the body.

In order to determine the blood glucose concentration level  $G_2(t)$  explicitly, we must first solve the differential Equation (3) and obtain an expression for  $G_1(t)$ . The result of the separation of the variables in Equation (3) is;

$$\int \frac{dG_1}{G_1} = \int -K_1 dt \Rightarrow \ln|G_1| = -K_1 t + d$$

$$G_1(t) = G_0 e^{-K_1 t} \quad (5)$$

Note that Equation (3) is a first order linear differential equation of the form:

$$\frac{dy(t)}{dt} + p(t)y(t) = q(t) \quad (6)$$

It has been verified in Ganesh and Balasubramanian, (2009) that:

$$y = e^{-\int p(t)dt} \left[ \int q(t)e^{\int p(t)dt} dt + C \right] \quad (7)$$

Equation (7) represent the solution to equation (6) where  $C$  is the constant. Substituting (5) into (4) gives a linear first order differential equation:

$$\frac{dG_2(t)}{dt} + K_2 G_2(t) = K_1 (G_0 e^{-K_1 t}) + K_2 G_0 \quad (8)$$

Equation (6) above has the following form of solution:

$$G_2(t) = e^{-\int K_2 dt} \left[ \int (K_1 G_0 e^{-K_1 t} + K_2 G_0) e^{\int K_2 dt} dt + C \right]$$

$$G_2(t) = G_0 \frac{K_1}{K_2 - K_1} (e^{-K_1 t} - e^{-K_2 t}) + G_0 \quad (9)$$

For SITT data, the insulin is administered intravenously and therefore the response of plasma glucose will be very fast, making  $K_2 \gg K_1$  at  $t > 0$ . Based on this, the above equation reduces to:

$$G_2(t) = G_0 e^{-K_1 t} + G_0 \quad (10)$$

Since the level of glucose changes with respect to the type of meal taken, it is represented by a system of linear differential equation. One major challenge in system identification is to estimate the unknown parameters and perform an SA to verify regions of the system and the most relevant state variables (Rodriguez-Fernandez and Banga, 2010). Estimating the unknown parameters of a mathematical model requires the input-output data and the class of model (Jacobs 2015). The parameters are chosen or guessed so that the output of the model is the best match with respect to the experimental data (Jacobs 2015).

## 2.2 Model Implementation

SensSB software toolbox was used for the model implementation. The model was implemented in 1.5 GHz core i3, 4.00GB RAM system. The study was begun with estimation of parameters then sensitivity analysis with local method then followed by global approaches based on DGSM and Sobol's method respectively.

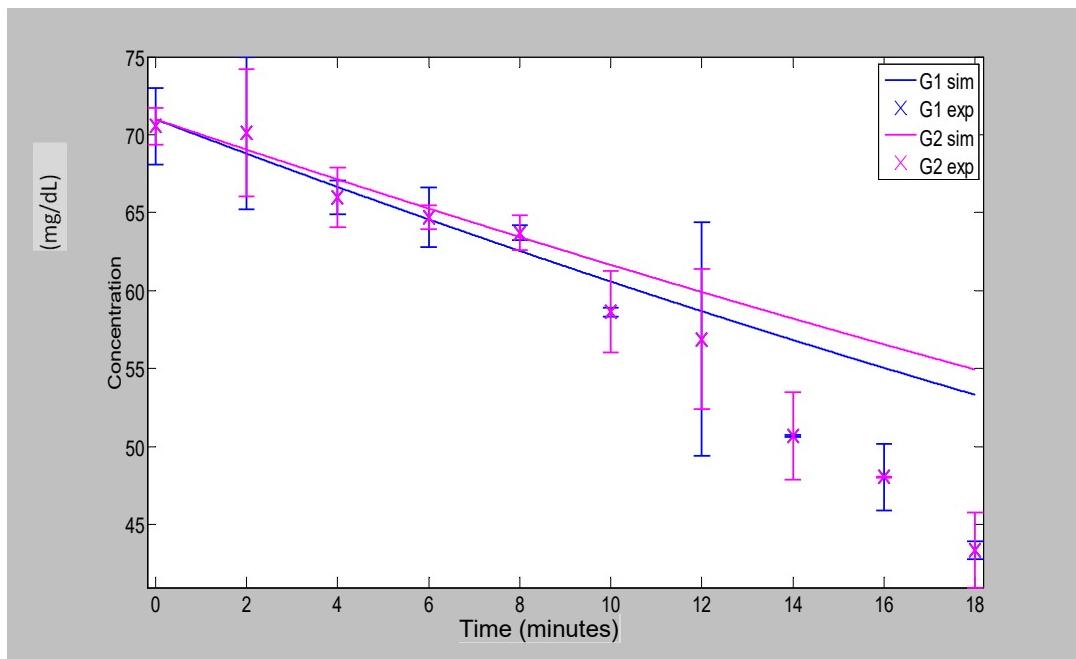
The SITT data was collected and rearranged into a single column such that it represented the output of the model. The algebraic model Equation (9) describing the SITT was developed and presented in section 2.1 above. In order to implement the model in SensSB software, it is necessary to formulate the problem so that it can accommodate the experimental data. The model equation was solved with the MATLAB solver ode15s and local sensitivities were calculated with SENS\_SYS. In the ordinary differential equations (ODEs) initialization stage, the necessary information to compute the function was provided, the SITT data had one state variable (plasma glucose concentration level) and the initial range for normoglycemic subject was taken as 70-80 mg/dL according to Diabetes Association of Nigeria (Chinenye, 2013). The data had 10 sampling points at [-10 0 2 4 6 8 10 12 14 16] measured in minutes. The system of ODEs involves 3 parameters, which are  $G_0$ ,  $K_1$ , and  $K_2$ . They were represented by p1, p2, and p3 respectively. The initial value chosen for the three parameters are [75 0.028 0.026], lower bound [60 0.01 0.01] and upper bound [80 0.03 0.03]. The 3 parameters are being estimated so the vector [1:3] equivalent to [1 2 3] were introduced as 'Index of the parameters to be modified', please mind that the upper and lower bounds are going to influence the value of the resulting global sensitivity analysis.

## 3. Results and Discussion

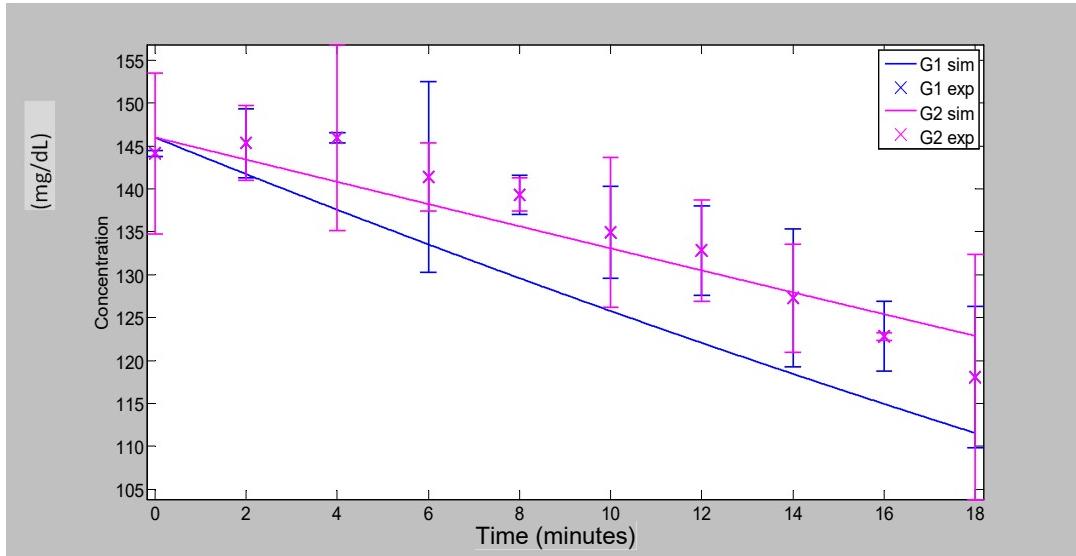
The results of the model identification, SA and Parameters estimation are presented and discussed in this section.

### 3.1 Dynamic model

The results obtained for the dynamic model described in Equations (3) and (4) was fitted on SITT data and shows an appreciable consistence with the level of blood glucose concentration measured during SITT experiment. The dynamic model results obtained was compared with Estela, (2011) results which indicates a better fit on the SITT data. Figures 2 and 3 shows a comparison between the model predicted values and the SITT data reported by Gutti *et al.* (2010), for a control and diabetic subject corresponding to the blood glucose concentration.



**Figure 2:** Fitted SITT data and the dynamic model for a control subject in SensSB.



**Figure 3:** Fitted SITT data and the dynamic model for diabetic subject in SensSB

It can be observed that the estimated parameters allow reproducing almost exactly the experimental data while all the local solvers that were tried with this initial point failed to converge, or converged

to bad local solutions. Different global solvers such as stochastic ranking evolutionary search (SRES) or differential equation (DE) also failed or converged in a much larger computational time.

### 3.2 Sensitivity analysis of the model

Here, the results for the sensitivity analysis of the model based on local, Sobol and DGSM method are presented. These are shown in Tables 1, 2 and 3, while their respective profile are shown in Figures 4, 5 and 6 respectively. The parameter ranking based on local, Sobol's and DGSM method are shown Figures 7, 8 and 9 respectively.

**Table 1:** Local sensitivity analysis results

Ranking	Parameter	msqr	Mabs	Mean	Min	Max	abs_sens
1	P2	1.16e-001	4.02e-002	-4.02e-002	5.58e-012	-4.65e-001	8.10e+001
2	P1	8.78e-002	4.29e-002	-4.85e-003	2.08e-001	-2.88e-001	1.59e+002
3	P3	0.00e+000	0.00e+000	0.00e+000	0.00e+000	0.00e+000	0.00e+000

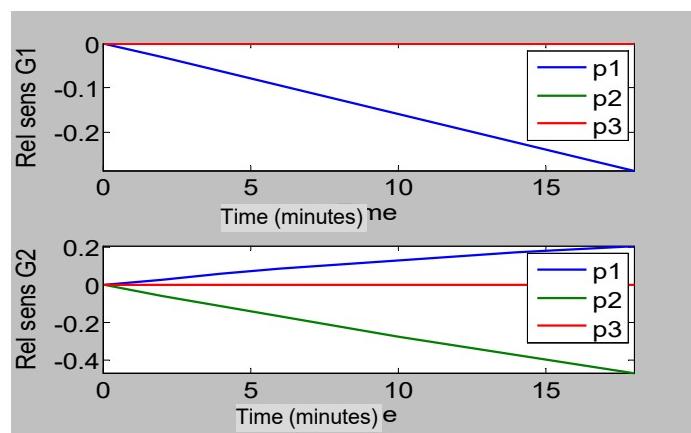
**Table 2:** Global sensitivity analysis results based on Sobol method

Parameter	SI_j	SI_j^T
P1	2.496e-001	8.293e-001
P2	7.504e-001	3.378e-001
P3	0.000e+000	0.000e+000

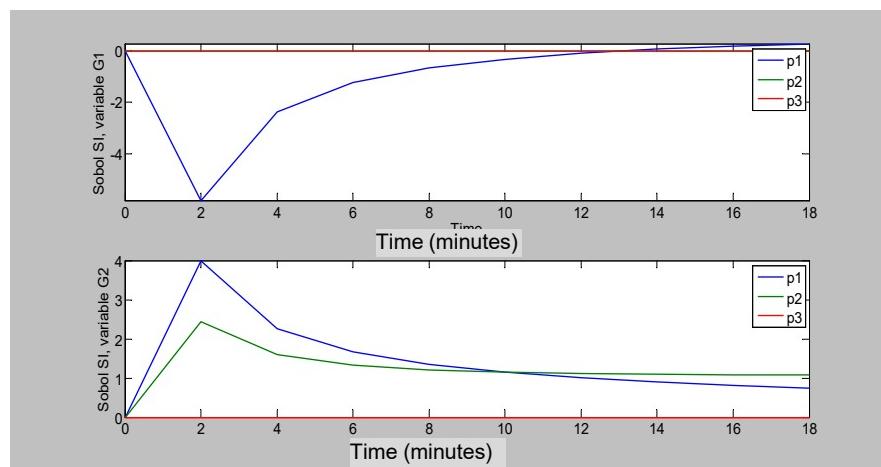
**Table 3:** Global sensitivity analysis results based on DGSM method

Parameter	abs_M_j^*	abs_sigma_j^*	rel_M_j^*	rel_sigma_j^*
P1	6.198e-001	6.160e-001	6.501e-001	6.219e-001
P2	3.802e-001	3.840e-001	3.499e-001	3.781e-001
P3	0.000e+000	0.000e+000	0.000e+000	0.000e+000

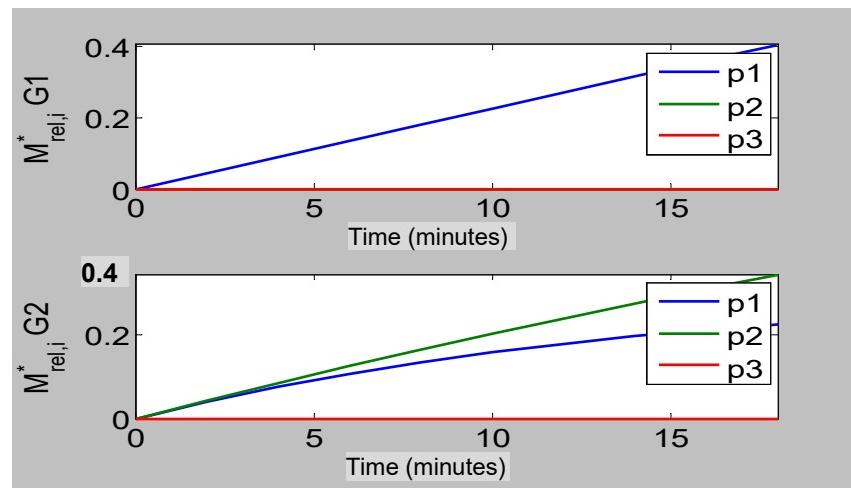
where: msqr is the parameter ranking based on the squared root of the square relative sensitivities, mabs is the parameter ranking based on the mean of the absolute values of the relative sensitivities, mean represent the parameter ranking based on the mean of the relative sensitivities, min is the ranking based on the minimum value of the relative sensitivities, max is the ranking based on the maximum values of the relative sensitivities and abs\_sens is the parameter ranking based on the mean of the absolute sensitivities.



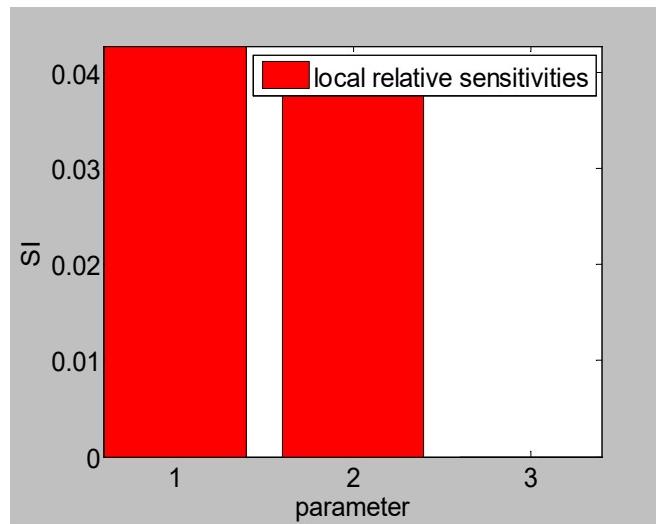
**Figure 4 :** Local sensitivity profile for dynamic model



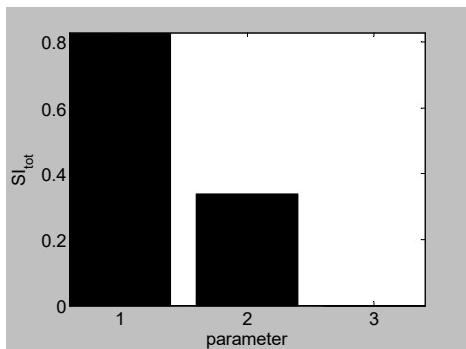
**Figure 5:** Sobol' profile for dynamic model.



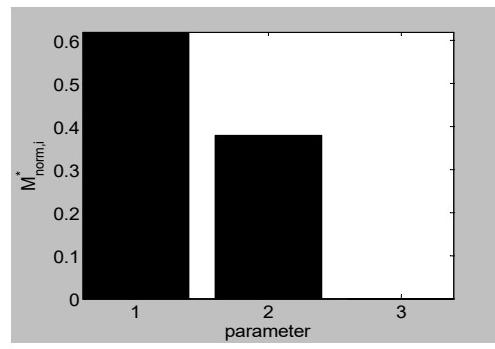
**Figure 6:** DGSM profile for dynamic model.



**Figure 7:** Parameter ranking based on local method



**Figure 8:** Parameter ranking based on Sobol' method



**Figure 9:** Parameter ranking based on DGSM method

As can be seen from the Figures 7, 8 and 9, parameter 3 shows a low relative sensitivity, which indicate the model is less sensitive to the third parameter. This is observable in both sensitivity analysis methods. Subsequently, local and global sensitivity analysis were conducted to determine the most sensitive parameter of the model identified in Section 2.1. It shows that the method can be easily implemented in MATLAB. The results of the sensitivity analysis further show that DGSM computations are reliable to a reasonable degree of accuracy, while Sobol's method ranked the parameters in order of importance.

### 3.3 Parameter estimation of the model

The results of the parameter estimation on local, Sobol' and DGSM method are presented in Tables 4, 5 and 6 respectively.

**Table 4:** Parameter estimation results based on local method

Optimal objective function value (least square) = 1.460e+000

CPU time required for the estimation = 3.24e+002sec

Parameter	Optimal value	Confidence interval (Cramer-Rao)
P1	1.500e-002	+2.689-004

P2	2.260e-002	+3.537e-004
P3	7.590e+001	$\infty$

**Table 5:** Parameter estimation results based on Sobol' method

Optimal objective function value (least square) = 1.216e+000

CPU time required for the estimation = 3.00e+002sec

Parameter	Optimal value	Confidence interval (Cramer-Rao)
P1	1.607e-002	+5.190e-004
P2	3.000e-002	+7.232e-004
P3	6.970e+001	$\infty$

**Table 6:** Parameter estimation results based on DGSM method

Optimal objective function value (least square) = 1.423e+000

CPU time required for the estimation = 3.01e+002sec

Parameter	Optimal value	Confidence interval (Cramer-Rao)
P1	1.620e-002	+4.931-004
P2	3.000e-002	+6.859e-004
P3	6.171e+001	$\infty$

The parameter estimated based on DGSM differ from those obtained using local and Sobol's method because DGSM depend on nominal values of the parameter. Estimated parameter values varies with different subjects and contradicts earlier reports by Sumner, (2010) who uses the principal components analysis to measure the importance of a parameter on the entire model output. The sensitivity analysis results presented in this work are based on the dynamic model of blood glucose concentration which is the goal of this study. The LSA and GSA based method are assessed on the basis of the length of the confidence intervals computed for the parameters with Cramer-Rao statistical method (Rodriguez-Fernandez and Banga, 2010) as shown in Tables 4, 5 and 6 in which the DGSM outperform both Sobol's and local methods.

#### 4 Conclusion

The prevalence of type II diabetes is increasing in Nigeria and globally and most of the mathematical models developed were devoted to the dynamic of glucose-insulin system based on Intravenous glucose tolerance test (IVGTT), oral glucose tolerance test (OGTT) and frequently sampled intravenous glucose tolerance test (FSIVGTT) data. This study proposed Short Insulin Tolerance Test (SITT) based model via optimal design of experiment. Our approach incorporates important steps required in model development process such as global sensitivity analysis, Pseudo-global identifiability analysis, Optimal experimental design based on global sensitivities, robust parameter estimation, etc. Techniques of global sensitivity analysis appear more appealing due to the fact that they investigate the entire range of parametric uncertainty. The parameters for the model developed were estimated in the least square sense with SITT data fitting the model satisfactorily. The result of local sensitivity was compared with Sobol' and DGSM and the values are assessed based on the length of confidence intervals with Cramer-Rao statistical replication.

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